

*Cont'd*  
isolating the host cells which express the MHC molecule.

*B7A*  
66. (amended) A single chain MHC class-II peptide comprising:  
a peptide-binding groove;  
covalently linked in sequence: 1) a class II  $\beta$  chain, 2) a single chain linker, and 3) a class  
II  $\alpha$  chain, wherein the chain of 1) or 3) or both 1) and 3) lack a functional transmembrane  
domain and the chain of 1) or 3) or both 1) and 3) are truncated compared to its respective full  
length chain; and  
a presenting peptide being covalently linked to the MHC molecule.

#### REMARKS

The undersigned wishes to thank Dr. DeCloux for the courtesy and helpful comments  
provided during their recent discussion of the application.

The specification has been amended to update the priority of the application, and claims  
52, 57-64 and 66 have been amended to address issues raised under Section 112, second  
paragraph and correct claim dependencies. No new matter has been added by virtue of the  
amendments.

Claims 53-55, 57-63, 66-69 and 71-76 were rejected under 35 U.S.C. 112, first  
paragraph.

The pending application fully satisfies the requirements of Section 112, including the  
written description requirements of Section 112, first paragraph.

The instant rejection appears to impose written description demands that far exceed what  
is required under Section 112, first paragraph. In this regard, attention is directed to Section 2163  
of the Manual of Examining Procedure which states in part:

The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement.

\* \* \*

The examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. 191 USPQ at 98 [*In re Wertheim*].

The *Wertheim* decision, cited at MPEP 2163.04 states the following (*In re Wertheim*, 191 USPQ at 98, copy enclosed; bold emphasis added):

**The PTO has done nothing more than argue a lack of literal support, which is not enough.** If lack of literal support alone were enough to support a rejection under §112, then the statement of *In re Lacack* [citation omitted] that "the invention as claimed does not have to be described *ipsis verbis* in order to satisfy the description requirement of §112," is empty verbiage. **The burden of showing that the claimed invention is not described in the specifications rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not *ipsis verbis* is insufficient.**

Indeed, the specification clearly supports the pending claims. For instance, at page 1, lines 4-9 of the application, the featured peptide binding groove is clearly disclosed:

For example, in one aspect, the invention relates to empty MHC complexes that contain a MHC molecule with a peptide-binding groove and a presenting peptide non-covalently linked to the MHC protein. In another aspect, the invention relates to MHC class II-peptide fusion complexes which include a single chain MHC class II molecule and a presenting peptide covalently linked to the peptide binding groove of the MHC protein.

Truncated MHC molecules such as recited in claims 53-60, 66-69 and 71-72 are described for instance at page 23, line 16 through page 24, line 5 of the application:

Truncated MHC fusion complexes contain a MHC molecule that is sufficiently truncated so the MHC fusion complex can be secreted into culture medium (e.g., physiological conditions; in the substantial or complete absence of detergent or the like) after expression. Thus, a truncated MHC fusion complex will not include regions rich in hydrophilic residues, typically the transmembrane and cytoplasmic domains of the MHC molecule, although at least portions of those domains may be suitably present provided the MHC molecule can be secreted as discussed. Thus, for example, for a preferred truncated DR1 MHC molecule, preferably from about residues 199 to 237 of the  $\beta$  chain and from about residues 193 to 230 of the  $\alpha$  chain of the MHC molecule are not included in the truncated MHC fusion complex. See the examples which follow. In addition to the sequences disclosed herein, sequences of domains of MHC class I and II molecules have been disclosed previously (see, e.g., the above mentioned publications). Truncated MHC fusion complexes of course also can be determined empirically, i.e. by examining if the MHC complex is secreted into culture medium after expression as discussed. Truncated MHC fusion complexes can be prepared by several means, e.g. expression of a soluble MHC molecule or enzymatic (e.g. papain) cleavage of at least portions of transmembrane and/or cytoplasmic domains of a full length MHC fusion complex.

Claims such as claims 61-63 and 74-75 that are directed multivalent MHC molecules are supported by disclosure such as page 29, line 20 to page 30, line 2 of the application:

Multivalent MHC fusion complexes or empty or loaded MHC molecules are desirable for a number of application. The valence of a MHC-antigenic peptide complex influences the effect of the complex on T cell receptor(s). For example, activation of the 3DT52.5 T cell hybridomas requires a MHC-antigenic molecule that has been made multivalent. Monovalent, soluble MHC complexes incapable of stimulating this T cell [J. McCluskey et al., *J. Immunology*, 141:1455 (1988)]. Desired multivalent MHC fusion complexes include those linked to an immunoglobulin, e.g., IgG, IgM or Fab'2. Chemically cross-linked MHC complexes (for example cross-linked to dendrimers) are also suitable multivalent species. For example, the MHC complex can be genetically modified by including sequences encoding amino acid residues with chemically reactive side chains such as Cys or His.

Similarly, tagged MHC molecules are fully disclosed in the application, such as at page 36, line 28 through page 37, line 5:

As an illustrative example, the sc-Iad/blank molecule can be modified with a detectable tag (e.g.,  $I^{125}$ , biotin or another protein tag disclosed herein) and then used to screen a random peptide library. Procedures for tagging proteins and screening libraries are well known [see, e.g., Sambrook et al., *supra* and Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, 1989; herein incorporated by reference].

The original claims also clearly support the present claims. See, for instance, original claims 1 through 29.

See also pages 3 through 8 of the application for even further support for the pending claims.

In view thereof, reconsideration and withdrawal of the rejection is requested.

Claims 53-55, 57-63, 66-69 and 71-76 were rejected under 35 U.S.C. 112, second paragraph.

A number of grounds of rejections have been obviated by the amendments made herein. For instance, claims 53 and 66 have been amended as generally recommended in the Office Action.

Applicants respectfully disagree that claims 74 and 75 lack antecedent basis for recitation of MHC molecules. Those claims recite "two or more" and hence the plural recitation of "molecules" is proper.

At page 6 of the Office Action, it is stated that the recitation in claim 66 of "presenting peptide covalently linked to the MHC molecule" is indefinite because it is not clear where the peptide is linked.

Applicants disagree. The skilled worker would fully understand the claim language, particularly when it is read in light of the supporting specification, as is proper. In this regard, attention is directed to the Manual of Patent Examining Procedure at Sections 2173.02 and 2173.04, which states in part:

When the examiner is satisfied that patentable subject matter is disclosed, and it is apparent to the examiner that the claims are directed to such patentable subject matter, he or she should allow the claims which define the patentable subject matter with a reasonable degree of particularity and definiteness. Some latitude in the manner of expression and aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire.

\* \* \*

Breadth of a claim is not to be equated with indefiniteness.

In view thereof, reconsideration and withdrawal of the rejection is thus requested.

Claims 53, 54, 55, 57, 58, 59, 61, 66, 67, 69 and 71 were rejected under the doctrine of obviousness-type double-patenting over certain claims of U.S. Patent 5,869,270.

Claims 68 and 72 also were rejected under the doctrine of obviousness-type double-patenting over a certain claim of U.S. Patent 5,869,270.

To expedite prosecution, an appropriate Terminal Disclaimer is submitted herewith, which is believed to obviate the rejections.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,



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**MARKED VERSION TO SHOW CHANGES**

53. (amended) A single chain class II MHC molecule comprising:  
a peptide-binding groove and  
covalently linked in sequence: 1) a class II  $\beta$  chain, 2) a single chain linker, and 3) a class II  $\alpha$  chain,

wherein the chain of 1) or 3) or both 1) and 3) lack a functional transmembrane domain  
and

the chain of 1) or 3) or both 1) and 3) are truncated compared to its respective [the] full  
length chain.

57. (amended) The MHC molecule of claim 53 [52], wherein the single chain  
linker is linked between the carboxyl terminus of the  $\beta$  chain and the amino terminus of the  $\alpha$   
chain.

58. (amended) The MHC molecule of claim 53 [52], wherein the  $\beta$  and  $\alpha$  chains  
are each independently selected from the group consisting of IE, IA, DR, DQ and DP proteins.

59. (amended) The MHC molecule of claim 53 [52] further comprising a  
presenting peptide non-covalently linked to a peptide binding groove of the MHC molecule.

60. (amended) The MHC molecule of claim 53 [52] wherein the MHC molecule  
is modified to carry a detectable tag.

61. (amended) A multivalent MHC complex comprising two or more linked MHC  
molecules of claim 53 [52].

62. (amended) A MHC complex of claim 61 [60] wherein the MHC molecules are  
linked to immunoglobulin domains.

63. (amended) A MHC complex of claim 61 [60] wherein the MHC complex is modified to carry a detectable tag.

64. (amended) A method for selecting host cells which express a single chain MHC class II molecule comprising:

introducing into host cells a cloning vector the comprises a DNA construct; encoding a single chain MHC class II molecule of claim [52] 53; culturing the host cells to express the MHC molecule; and isolating the host cells which express the MHC molecule.

66. (amended) A single chain MHC class-II peptide comprising:  
a peptide-binding groove;  
covalently linked in sequence: 1) a class II  $\beta$  chain, 2) a single chain linker, and 3) a class II  $\alpha$  chain, wherein the chain of 1) or 3) or both 1) and 3) lack a functional transmembrane domain and the chain of 1) or 3) or both 1) and 3) are truncated compared to its respective [the] full length chain; and  
a presenting peptide being covalently linked to the MHC molecule.